ORIGINAL INVESTIGATION

Mortality and Cancer Incidence Among Individuals With Down Syndrome

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Background: Individuals with Down syndrome (DS) have a predisposition to leukemia and possibly other cancers and excess mortality from other conditions, but information on the magnitude of risk associated with specific cancers or causes of death is sparse.

Methods: Mortality experience and cancer incidence were evaluated in a combined cohort of 4872 individuals with a hospital discharge diagnosis of DS in Sweden (1965-1993) or Denmark (1977-1989) by linkage to national cancer and vital statistics registries. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were estimated by comparison with age, sex, and calendar-year expected values.

Results: Individuals with DS had an increased risk of incident acute lymphocytic (SIR, 24.2; 95% confidence interval [CI], 15.2-36.6; n=22) and acute nonlymphocytic (SIR, 28.2; 95% CI, 15.7-48.3; n=14) leukemias. Risks of testicular cancer (SIR, 3.7; 95% CI, 1.0-9.4; n=4) and liver cancer (SIR, 6.0; 95% CI, 1.2-17.5; n=3) were also elevated. Individuals with DS also experienced elevated mortality attributed to stomach cancer (SMR, 6.4; 95% CI, 1.7-16.4; n=4), dementia and Alzheimer disease (SMR, 54.1; 95% CI, 27.9-94.4), epilepsy (SMR, 30.4; 95% CI, 13.9-57.7), ischemic heart disease (SMR, 3.9; 95% CI, 2.7-5.4), other heart disease (SMR, 16.5; 95% CI, 11.0-23.7), cerebrovascular disease (SMR, 6.0; 95% CI, 3.5-9.6), infectious diseases (SMR, 12.0; 95% 6.0-21.4), and congenital anomalies (SMR, 25.8; 95% CI, 21.0-31.4).

Conclusions: Individuals with DS have a substantially increased risk of mortality due to specific causes and may have an elevated risk of other incident cancers in addition to leukemia. These results provide clues regarding chromosome 21 gene involvement in diseases that complicate DS and are important for disease detection and care of affected individuals.

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DOWN SYNDROME (DS) occurs in 1 of every 800 to 1000 live births[1,2] and is associated with trisomy of chromosome 21, except in rare instances of chromosome 21 translocation (4%-5% of all cases) or mosaicism (2%-4%).[1,3] Individuals with DS have an increased risk of developing acute leukemia[4-6] and excess mortality due to infectious agents, congenital anomalies, and other conditions.[1,3] Evaluation of cancer risks and the mortality experience of individuals with DS is important for their clinical care and for the early detection of associated diseases. Large cohort studies of DS have been rare, however, and often include only institutionalized individuals, who may not represent the more general DS population. Thus, although many conditions are reported to occur excessively among individuals with DS,[7,8] epidemiologic evidence in support of some associations has been limited.

New opportunities to understand conditions that occur excessively among persons with DS have arisen owing to the full sequencing of chromosome 21, making it possible to identify disease-related loci among a relatively small number of candidate genes (approximately 225), more than half of which correspond to known genes.[9] The increased risks of specific diseases among DS-affected individuals may be related to the overexpression of particular chromosome 21 genes, such as oncogenes or growth factors, or to the presence of an extra chromosome 21 that may affect development or cell homeostasis. Several genes on chromosome 21 have been implicated in disorders complicating DS, including *AML1* in acute myeloid leukemia[10] and amyloid protein precursor (*APP*) in early-onset Alzheimer disease,[11] and are also linked to the same conditions in the absence of DS. In addition, the predisposition to infectious diseases, leukemia, and other disorders among in-

Table 1. Characteristics of 4872 Individuals With a Hospital Discharge Diagnosis of Down Syndrome in Sweden (1965-1993) and Denmark (1977-1989)*

Characteristic	Sweden (n = 3359)	Denmark (n = 1513)
Sex		
M	1815 (54.0)	807 (53.3)
F	1544 (46.0)	706 (46.7)
Year of birth		
Before 1965	1184 (35.2)	563 (37.2)
1965-1974	676 (20.1)	299 (19.8)
1975-1984	765 (22.8)	412 (27.2)
1985-1993†	734 (21.9)	239 (15.8)
Age at cohort entry, y‡		
1-4	1816 (54.1)	658 (43.5)
5-9	242 (7.2)	118 (7.8)
10-19	329 (9.8)	228 (15.1)
≥20	972 (28.9)	509 (33.6)
Year of cohort entry		
Before 1975	581 (17.3)	0
1975-1984	1421 (42.3)	1030 (68.1)
1985-1993†	1357 (40.0)	483 (31.9)
Length of follow-up, y		
1-4	814 (24.2)	142 (9.4)
5-9	813 (24.2)	490 (32.4)
10-14	722 (21.5)	482 (31.9)
≥15	1010 (30.1)	399 (26.4)
Age at cohort exit, y		
1-9	907 (27.1)	325 (21.5)
10-19	748 (22.2)	368 (24.3)
20-29	612 (18.2)	292 (19.3)
30-39	346 (10.3)	166 (11.0)
40-49	305 (9.1)	156 (10.3)
≥50	441 (13.1)	206 (13.6)
Follow-up, mean, y	10.5	10.1
Total person-years, No.	32 046	13 714

*Data are given as number (percentage) except where otherwise indicated.
†The last year of cohort entry for Danish individuals was 1989.
‡Individuals with Down syndrome were not included in the cohort until 1 year after hospital discharge.

dividuals with DS may be related to interactions between genes and environmental exposures, providing hints regarding exposures that merit investigation as modifiers of genetic risk.

The availability of hospital discharge records throughout Sweden and Denmark and national registration numbers provided to each resident presented a rare opportunity to identify all individuals with a discharge diagnosis of DS and, by linkage of these data to national registries, to estimate cancer incidence and mortality risks.

METHODS

STUDY COHORT

The Swedish Inpatient Register and the Danish Hospital Discharge Register, 2 national record systems, served as the source of identification of all patients. A national registration number, provided to all residents of Sweden since 1947 and Denmark since 1968, was used to link hospitalization data to population-based registries of mortality and cancer incidence. The Swedish Inpatient Register was initiated in 1964 with coverage in a defined catchment area and included 60% of the Swedish population in 1969, 75% in 1978, 85% at the end of 1983, and 100% since 1987. The Danish Hospital Discharge Register began with national coverage in 1977. We identified all individuals with a hospital discharge diagnosis of DS recorded in the Swedish Inpatient Register between 1965 and 1993 (*International Classification of Diseases, Seventh Revision* [*ICD-7*], code 325.4; *ICD-8* codes 310.50-310.51, 311.50-311.51, 312.50-312.51, 313.50-313.51, 314.50-314.51, and 315.50-315.51; and *ICD-9* code 758A) and in the Danish Hospital Discharge Register between 1977 and 1989 (*ICD-8* codes 310.50-310.51, 311.50-311.51, 312.50-312.51, 313.50-313.51, 314.50-314.51, 315.50-315.51, and 759.30-759.39). The ethics committee of Uppsala University, the Swedish Data Inspection Board, Stockholm, Sweden, and the Danish Data Protection Board, Copenhagen, Denmark, reviewed and approved this study.

FOLLOW-UP

Individual hospitalization records were linked to the Swedish and Danish population, migration, cancer incidence, and mortality registries using the national registration number. Follow-up began 12 months after the first hospital discharge for DS during the study, regardless of any previous hospitalizations. All deaths and incident cancers, as well as follow-up time, that occurred within 12 months of the initial hospitalization were excluded to minimize selection bias. Individuals with a hospital discharge diagnosis of DS were followed until death, emigration, or the end of follow-up (December 31, 1993), whichever occurred first. Of the 4337 identified records in Sweden, 978 were ineligible: 974 had less than 1 year of follow-up (primarily due to cohort entry in 1993), 2 had inconsistent sexes, and 2 had inconsistent dates. We also identified an additional 582 hospitalizations with national registration numbers that were either incomplete or duplicate or that did not match with any living, dead, or emigrated person. Some of these records are likely to represent single hospitalizations of already registered cohort members, and others may represent unique individuals. In the absence of valid national registration numbers, follow-up through record linkages was impossible, and these records were therefore excluded. Of the 1729 identified patients in Denmark, 216 were ineligible: 215 because they were followed up for less than 1 year and 1 because of an inconsistent date.

STATISTICAL ANALYSIS

The expected cancer incidence and mortality rates were calculated by multiplying the observed number of person-years in each country (within categories according to sex and 5-year age and calendar intervals) by the cancer site incidence and underlying cause-specific mortality rates for each category and country. Multiple primary tumors were included in the analysis (n=3). Standardized incidence ratios and standardized mortality ratios, defined as the ratios of observed-expected numbers of incident cancers or deaths, respectively, were used to estimate relative risk. The 95% confidence intervals of the standardized incidence ratio and the standardized mortality ratio were calculated under the assumption that the number of observed cancers or deaths follows a Poisson distribution.[12] Leukemia and solid tumor risks were assessed further according to sex and age at diagnosis.

RESULTS

A combined cohort of 4872 individuals (2622 males and 2250 females) from Sweden and Denmark received a hospital discharge diagnosis of DS during the study and survived at least 12 months after the date of discharge (**Table 1**). Approximately 50% of the cohort was younger

Table 2. Standardized Incidence Ratios (SIRs) and 95% Confidence Intervals (CIs) for Selected Primary Cancers Among Individuals With a Hospital Discharge Diagnosis of Down Syndrome in Sweden (1965-1993) and Denmark (1977-1989)

	Sweden		Denmark		Total	
Incident Cancer	Observed, No.	SIR (95% CI)	Observed, No.	SIR (95% CI)	Observed, No.	SIR (95% CI)
Overall	37	1.5 (1.1-2.1)	30	1.9 (1.3-2.7)	**67**	1.7 (1.3-2.1)
All hematopoietic cancers	19	6.5 (3.9-10.2)	20	14.3 (8.7-22.1)	**39**	9.1 (6.4-12.4)
Lymphoma	1	0.7 (0.1-4.0)	1	1.4 (0.1-8.1)	**2**	1.0 (0.1-3.5)
Non-Hodgkin lymphoma	1	1.1 (0.1-5.6)	1	2.2 (0.1-12.4)	**2**	1.5 (0.2-5.4)
All leukemias	18	13.9 (8.2-23.0)	19	31.1 (18.7-48.6)	**37**	19.5 (13.7-26.8)
Acute leukemia	17	18.1 (10.5-29.0)	19	41.3 (24.9-64.5)	**36**	25.8 (18.1-35.7)
Lymphocytic	9	14.2 (6.5-27.0)	13	47.2 (25.1-80.7)	**22**	24.2 (15.2-36.6)
Nonlymphocytic	8	25.9 (11.2-51.1)	6	33.6 (12.3-73.2)	**14**	28.2 (15.7-48.3)
Leukemia, unspecified	1	9.0 (0.1-50.0)	0	(0-164.2)	**1**	33.3 (0.8-185.6)
All solid tumors	18	0.9 (0.5-1.3)	10	0.7 (0.3-1.3)	**28**	0.8 (0.5-1.1)
Stomach	2	3.5 (0.4-12.7)	1	3.9 (0.1-21.4)	**3**	3.5 (0.7-10.2)
Small intestine	1	10.6 (0.1-59.1)	0	(0-126.3)	**1**	8.3 (0.2-46.4)
Colon	2	1.7 (0.1-6.0)	2	2.7 (0.3-9.6)	**4**	2.1 (0.6-5.3)
Liver	3	7.3 (1.5-21.4)	0	(0-35.3)	**3**	6.0 (1.2-17.5)
Breast	2	0.6 (0.1-2.0)	1	0.4 (0.1-2.3)	**3**	0.5 (0.1-1.4)
Endometrial	1	1.9 (0.1-10.5)	1	2.5 (0.1-14.0)	**2**	2.2 (0.3-7.8)
Testis	2	3.4 (0.4-12.3)	2	3.9 (0.4-13.9)	**4**	3.7 (1.0-9.4)
Other male genital*	2	43.2 (4.9-156.0)	1	50.4 (0.7-280.5)	**3**	45.5 (9.3-132.8)
Kidney	1	1.4 (0.1-7.5)	0	(0-9.9)	**1**	0.6 (0.1-3.4)
Brain	1	0.5 (0.1-2.7)	1	1.0 (0.1-5.3)	**2**	0.7 (0.1-2.4)
Endocrine	1	1.5 (0.1-8.4)	0	(0-100.6)	**1**	1.4 (0.1-8.0)
Unspecified	0	(0-6.8)	1	0.7 (0.1-3.8)	**1**	0.6 (0.1-3.2)

*All 3 were penile cancer.

Table 3. Standardized Incidence Ratios (SIRs) and 95% Confidence Intervals (CIs) for Selected Primary Cancers Among Individuals With a Hospital Discharge Diagnosis of Down Syndrome in Sweden (1965-1993) and Denmark (1977-1989), by Age at Cancer Diagnosis

		Solid Tumors		Acute Leukemia	
Age at Cancer Diagnosis, y	Person-Years, No.	Observed, No.	SIR (95% CI)	Observed, No.	SIR (95% CI)
1-4	6978	1	1.2 (0.1-6.5)	27	61.4 (40.4-89.3)
5-9	8398	0	(0-6.0)	2	7.7 (0.9-27.8)
10-14	7087	0	(0-6.3)	3	21.4 (4.4-62.6)
15-19	5822	0	(0-4.6)	3	33.3 (6.8-97.4)
≥20	17 722	27	0.8 (0.5-1.2)	1	2.6 (0.1-14.7)

than 5 years at hospital discharge; 30% were 20 years or older.

CANCER INCIDENCE

During follow-up, 67 individuals with DS developed incident cancers (**Table 2**).[13] Of these, 36 (54%) were acute leukemias. The risk of all leukemias combined was increased approximately 20-fold. Risks of developing acute lymphocytic leukemia or acute nonlymphocytic leukemia were roughly equal, with each occurring approximately 26 times more frequently than in the general population. In the overall study cohort, 28 solid tumors were observed (vs 36.2 expected). Individuals with DS had a modestly elevated risk of cancers of the liver and testes, based on only a few cases at each site. Three of the 4 testicular neoplasms were seminomatous germ cell tumors, and the histologic origin of the fourth tumor was unknown. Risk of other male genital cancers was also elevated, based on 3 cases of penis cancer. Other cancers that were observed included non-Hodgkin lymphoma (n=2), stomach cancer (n=3), cancer of the small intestine (n=1), colon cancer (n=4), breast cancer (n=3), endometrial cancer (n=2), brain tumor (n=2), kidney cancer (n=1), and endocrine tumor (a parathyroid adenoma) (n=1).

All but 1 leukemia case was diagnosed before age 20 years, but only 1 solid tumor (a kidney cancer at age 1 year) was diagnosed before age 20 years (**Table 3**).[13] The altered risks of leukemia and solid tumors did not differ by sex (data not shown). Although solid tumor risk estimates were similar in Danish and Swedish individuals, the acute leukemia standardized incidence ratios were somewhat higher in the Danish cohort.

MORTALITY

Individuals with DS had an almost 8-fold increased risk of mortality from all causes during follow-up when deaths ascribed to DS itself (*ICD-9* code 758) were excluded

Table 4. Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals (CIs) for Selected Medical Conditions Among Individuals With a Hospital Discharge Diagnosis of Down Syndrome in Sweden (1965-1993) and Denmark (1977-1989)

		Sweden		Denmark		Total	
ICD-9 Codes	Underlying Cause of Death	Observed, No.	SMR (95% CI)	Observed, No.	SMR (95% CI)	Observed, No.	SMR (95% CI)
. . .	All causes, excluding *ICD-9* code 758*	331	7.8 (6.9-8.6)	184	7.8 (6.7-9.0)	**515**	7.8 (7.1-8.5)
. . .	All causes, including *ICD-9* code 758	492	11.4 (10.4-12.5)	250	10.5 (9.3-11.9)	**742**	11.1 (10.3-11.9)
001-139	Infectious diseases	8	15.4 (6.6-30.3)	3	7.3 (1.5-21.4)	**11**	12.0 (6.0-21.4)
140-208	Malignant neoplasms†	29	3.3 (2.2-4.8)	28	4.6 (3.1-6.6)	**57**	3.9 (2.9-5.0)
151	Stomach	3	7.0 (1.4-20.4)	1	5.1 (0.1-28.2)	**4**	6.4 (1.7-16.4)
153	Colon	1	1.9 (0.1-10.7)	2	5.1 (0.6-18.3)	**3**	3.3 (0.7-9.6)
155	Liver	1	4.9 (0.6-27.2)	1	14.9 (0.2-82.9)	**2**	7.2 (0.9-26.1)
156	Gallbladder	2	10.6 (1.2-38.1)	0	(0-68.3)	**2**	8.2 (1.0-29.6)
157	Pancreas	1	2.2 (0.1-12.1)	0	(0-14.7)	**1**	1.4 (0.1-7.8)
186	Testis	1	24.0 (0.3-133.3)	1	26.4 (0.3-146.6)	**2**	25.2 (3.0-90.9)
202	Non-Hodgkin lymphoma	1	3.0 (0.1-16.7)	1	5.7 (0.1-31.6)	**2**	3.9 (0.5-14.2)
204-208	Leukemia	16	22.1 (12.6-35.9)	19	56.8 (34.2-88.7)	**35**	33.2 (23.1-46.2)
. . .	Other/unspecified‡	3	0.6 (0.1-1.7)	3	0.7 (0.1-2.0)	**6**	0.6 (0.2-1.4)
250	Diabetes mellitus	5	10.2 (3.3-23.8)	4	13.1 (3.5-33.4)	**9**	11.4 (5.2-21.6)
240-249, 251-279	Other endocrine or metabolic disorders	0	(0-12.3)	2	10.9 (1.2-39.3)	**2**	3.4 (0.4-12.5)
290, 331§	Dementia or Alzheimer disease	10	50.3 (24.1-92.5)	2	83.5 (9.4-301.4)	**12**	54.1 (27.9-94.4)
320-389 (excluding 331)§	Diseases of the nervous system	22	19.9 (12.5-30.2)	3	5.5 (1.1-16.1)	**25**	15.2 (9.8-22.4)
324	Intracranial abscess	7	1048.3 (419.9-2160.1)	2	251.9 (28.3-909.6)	**9**	612.2 (279.5-1162.2)
345	Epilepsy	9	40.6 (18.5-77.0)	0	(0-48.5)	**9**	30.4 (13.9-57.7)
410-453	Diseases of the circulatory system	70	6.4 (5.0-8.1)	26	5.7 (3.7-8.3)	**96**	6.2 (5.0-7.6)
410-414	Ischemic heart disease	24	3.7 (2.4-5.6)	12	4.3 (2.2-7.5)	**36**	3.9 (2.7-5.4)
420-429	Other heart disease	21	15.5 (9.6-23.7)	8	19.6 (8.5-38.7)	**29**	16.5 (11.0-23.7)
430-439	Cerebrovascular disease	13	6.6 (3.5-11.2)	4	4.7 (1.3-11.9)	**17**	6.0 (3.5-9.6)
440-453	Arterial, veins, and thromboembolic	8	9.6 (4.2-19.0)	2	8.3 (0.9-30.1)	**10**	9.3 (4.5-17.2)
460-519	Respiratory tract disease	92	49.9 (40.2-61.2)	43	43.7 (31.6-58.8)	**135**	48.6 (40.7-57.5)
480-486	Pneumonia	80	78.4 (62.1-97.4)	21	105.8 (65.5-161.8)	**101**	82.8 (67.4-100.6)
466, 490-491	Bronchitis	5	21.9 (7.0-51.0)	15	29.4 (16.5-48.6)	**20**	27.1 (16.5-41.8)
487	Influenza	1	29.8 (0.4-165.6)	4	340.7 (91.7-872.2)	**5**	108.7 (35.0-253.7)
520-579	Diseases of the digestive system	13	10.1 (5.4-17.2)	7	7.9 (3.2-16.3)	**20**	9.2 (5.6-14.2)
531-534	Gastric or duodenal ulcer	2	13.0 (1.5-47.1)	2	22.3 (2.5-81.5)	**4**	16.7 (4.5-42.9)
571	Cirrhosis of the liver	2	3.6 (0.4-12.9)	3	5.2 (1.0-15.1)	**5**	4.4 (1.4-10.3)
580-629	Diseases of the genitourinary system	11	39.2 (19.5-70.1)	4	30.3 (8.2-77.6)	**15**	36.3 (20.3-59.9)
590	Nephritis	2	28.8 (3.2-103.8)	0	(0-102.5)	**2**	18.9 (2.3-68.1)
740-779 (excluding 758)	Congenital anomalies	49	19.1 (14.1-25.2)	50	39.4 (29.2-51.9)	**99**	25.8 (21.0-31.4)
745-747	Heart/circulatory system	46	37.4 (27.4-49.9)	48	67.2 (49.6-89.1)	**94**	49.5 (40.0-60.5)
748-757, 759-779	Other (excluding 758)‡	3	2.2 (0.5-6.5)	2	3.6 (0.4-13.1)	**5**	2.6 (0.8-6.1)
800-999	External causes	16	1.8 (1.0-2.9)	6	1.3 (0.5-2.8)	**22**	1.6 (1.0-2.4)

Abbreviation: *ICD-9, International Classification of Diseases, Ninth Revision.*

*Deaths that were attributed to Down syndrome itself (*ICD-9* code 758) were not included in either the "all-cause" or "congenital anomalies" mortality risk calculations.

†Cancer deaths and incident cancers do not include the same individuals because some cancers were incident within a year of hospital discharge or before the study follow-up began.

‡Other neoplasms cited as underlying causes of death included 1 bone sarcoma, 3 of unknown primary sites, and a single case each of polycythemia vera and myelofibrosis, which were considered malignancies under *ICD-8*.

§Under *ICD-9*, dementia and Alzheimer disease were coded under "nervous system conditions," whereas under *ICD-8* they were not. Thus, "nervous system conditions" are presented herein with exclusion of dementia and Alzheimer disease.

(**Table 4**). The increases in mortality were generally similar in the 2 countries, although some differences were apparent when case numbers were small. Mortality due to infectious diseases was 12 times greater than expected, with septicemia and infectious hepatitis being the most common underlying cause of death (6 of 11 deaths). Mortality from malignant neoplasms was elevated 4-fold, primarily owing to leukemia, although there were also excesses owing to cancers of the stomach, liver, and gallbladder, based on small numbers. Persons with DS also

experienced excess mortality due to diabetes mellitus, dementia (including Alzheimer disease), and neurologic conditions such as epilepsy and intracranial abscess.

In addition, individuals with DS had a 4- to 16-fold excess risk of mortality from ischemic heart disease, other forms of heart disease, cerebrovascular disease, and venous thromboembolic disorders. Substantial increases in mortality were also attributed to respiratory diseases, notably pneumonia, bronchitis, and influenza. Also evident was excess mortality from gastric and duodenal ulcers and cirrhosis of the liver. There was considerably elevated mortality due to congenital anomalies, primarily of the heart and circulatory system. Deaths ascribed to DS itself (*ICD-9* code 758; n = 227) were not included among the anomalies. The risk of death due to a variety of external causes was also increased.

COMMENT

In this cohort study of individuals with DS, there was an elevated risk of incident leukemia and liver, testicular, and penile cancers compared with the general population. In addition, overall mortality risks were almost 8-fold higher for individuals with DS, reflecting increased mortality attributed to leukemia and a variety of nonneoplastic conditions.

Our findings should be considered in light of possible methodologic limitations of the study. In particular, individuals with DS who were identified through a hospital register may constitute a selected population with a greater risk of mortality and cancer incidence than those not hospitalized. However, the substantially increased mortality risks observed in this study are less likely to be explained entirely by selection bias, an effect that should have been mitigated by the exclusion of all deaths and incident cancer diagnoses in the 12 months subsequent to discharge. We also could not take into account exposures such as smoking, nutrition, body mass index, physical activity, and infectious agents that may have contributed to the variations in disease risk, particularly among those with DS who were institutionalized.

The 12-fold excess mortality attributed to infectious diseases in this study may be associated with the impaired cellular and humoral immunity that has been described in individuals with DS, including lower or abnormal levels of total lymphocytes[14,15] or specific T- or B-cell subpopulations,[14,16,17] as well as a reduced proliferative response to mitogen challenge,[14,16] compared with age-matched controls. Viral or bacterial infections were cited as the underlying cause for approximately one fifth of all deaths in this cohort and included those classified under *ICD-9* as respiratory diseases (such as pneumonia, bronchitis, and influenza) and intracranial abscesses.[18]

The 26-fold increases in the risk of incident acute lymphocytic leukemia and acute nonlymphocytic leukemia in this cohort are consistent with the elevated relative risks and confidence limits noted in previous cohort studies in Norway[6] and the United States.[19,20] Risk was highest among those aged 1 to 4 years, but it remained elevated compared with background rates until age 20 years. Our Danish study population includes some individuals with DS identified from the Danish Cytogenetics Registry who were recently reported to have an elevated risk of leukemia.[21] In nested case-control studies[22,23] using Swedish birth registry data, children who developed myeloid or lymphatic leukemia were substantially more likely to have DS, and a few children in those studies were included in our study population. The sharply elevated risk of acute leukemias in DS may be due in part to the additional copy of *AML1,* a leukemia-associated oncogene present on chromosome 21. Translocations involving *AML1* (found in 13% of acute myeloid leukemias[24] and 27% of acute lymphocytic leukemias[25]) and chromosomal abnormalities such as acquired trisomy 21[26] (found in 27% of acute myeloid leukemias and 16% of acute lymphocytic leukemias[27]) are commonly seen in acute leukemias that arise in children without DS. Because the extra copy of *AML1* alone is not sufficient to cause acute leukemia in all individuals with constitutional trisomy 21, additional genetic or environmental factors are probably involved.

Individuals with DS in our study had an increased risk of incident liver cancer and elevated mortality due to stomach, liver, and gallbladder cancers, although these risk estimates were based on few observations. Previous studies[28,29] have reported few cancers at these sites, possibly because they did not include many individuals with DS who had reached the older ages at which these cancers tend to occur. In one study,[30] an excess of gastric cancer was observed, based on 2 cases in males. Although our study population was identified through hospital discharge diagnoses, which might overestimate some cancer risks, such methods seem unlikely to result in an elevated risk of these relatively uncommon cancers, particularly in the face of somewhat reduced risks for all solid tumors combined. The excess risk of liver cancer may be attributable in part to infection with the hepatitis B virus,[31] which also may be implicated in the elevated mortality from liver cirrhosis[32] observed in this cohort. Among institutionalized and noninstitutionalized individuals, those with DS have a higher prevalence of chronic hepatitis B infection than those with mental retardation.[33,34] Similarly, the increased stomach cancer mortality possibly could be related to chronic infection by *Helicobacter pylori*,[35] a bacterium also linked to gastric and duodenal ulcers,[36] which also occurred more frequently than expected in our mortality analysis. Infection with the hepatitis B virus and *H pylori* may be heightened by transmission within institutionalized settings[37] and by the altered cellular and humoral immunity evident in individuals with DS.[14-16]

The increased risk of testicular cancer in our study is consistent with the excess of testicular seminomas suggested in some clinical surveys of DS.[38,39] Undescended testes, a risk factor for testicular cancer, is more common than expected in DS (relative risk, 37).[40] However, in 2 comparative genomic hybridization studies, 63% to 90% of non-DS seminomatous germ cell tumors demonstrated a gain of 21q,[41,42] suggesting that chromosome 21 gene expression might predispose to testicular cancer development independent of undescended testes. Risk of penile cancer was also increased in our study. Poor personal hygiene and infections such as human papilloma

virus are risk factors for this tumor,[43] which has not previously been associated with DS.

Risk of solid tumors other than gastrointestinal and male genital tumors was somewhat reduced in our study population, as suggested by 2 other surveys[38,44] of cancer in individuals with DS. Although it has been proposed that the slightly lower risk may be related to the increased expression of chromosome 21 tumor suppressor genes, it seems likely that decreased tobacco and alcohol use, early menopause,[45] and other environmental and host factors associated with DS also contributed.

Individuals with DS have previously been reported[46,47] to be at increased risk for diabetes mellitus, particularly type 1 diabetes mellitus, and the elevated diabetes mellitus mortality rate in the present study was also observed in another study.[48] Age at onset of diabetes mellitus may be earlier among those with DS than in other populations.[47,49] The autoimmune regulator gene *AIRE* (also known as *APECED*) on chromosome 21 may be related to familial aggregation of type 1 diabetes mellitus, but it did not seem to play a role in diabetes mellitus associated with DS in one study.[49]

During a portion of the study, the *ICD* codes used to identify causes of mortality did not distinguish Alzheimer disease from other forms of dementia; thus, only the substantially elevated risk of dementia (which includes Alzheimer disease) is presented. In a previous study,[48] individuals with DS also had elevated mortality ascribed to Alzheimer disease. Previous studies[50-52] have indicated that Alzheimer disease or dementia is more common in individuals with DS than in those with other types of mental disability. The prevalence of dementia in persons with DS aged 50 to 59 years ranged from 42% to 55% in 2 studies[51,52] and did not seem attributable to selective institutionalization.[52] The amyloid A4 precursor protein, produced by the *APP* gene on chromosome 21, has been found to accumulate in the brains of patients with DS at much younger than expected ages.[53] Inherited alterations in this protein also have been found in a small proportion of multiplex families with Alzheimer disease.[11]

The increased mortality attributed to epilepsy in our study is in accord with the high prevalence of epilepsy (8%-17%) previously reported in adults with DS[52,54] and with the elevated mortality attributed to epilepsy in a British study.[48] Epilepsy has been noted more often in the subset of individuals with DS who have been diagnosed as having dementia or Alzheimer disease,[52] a relationship also seen in the general population.[55] A gene related to progressive myoclonus epilepsy (*EPM1*), a rare autosomal recessive disorder with early onset, is located on chromosome 21[56] and may contribute to the childhood epilepsy diagnoses also evident in those with DS.[54]

The excess mortality from cardiovascular disease in our cohort has been frequently described in DS populations,[3,28,48] but it may sometimes be a consequence of congenital heart malformations, which are coded separately under congenital anomalies in *ICD-9*. The 4- to 16-fold increased risks of other types of heart disease in our study may be related to unrecognized congenital heart defects[3] and increased body mass index,[8] lower physical activity, and a tendency toward diabetes mellitus among individuals with DS.[46-48] In addition, the risk of coronary heart disease seems elevated in individuals who harbor particular infectious agents, including *Chlamydia pneumoniae*,[57,58] and the greater risks of pneumonia, influenza, and other infections in those with DS[8,28] may have contributed to the increased cardiovascular disease mortality. The elevated mortality from cerebrovascular disease in this cohort may be related in part to deposition of the β-amyloid protein produced by the chromosome 21 *APP* gene, a condition known as cerebral amyloid angiopathy, which is often complicated by cerebrovascular hemorrhage.[59,60]

The substantially increased risk of mortality from congenital malformations in our study is in agreement with previous investigations, which have documented an elevated prevalence at birth or elevated mortality due to anomalies of the cardiovascular, gastrointestinal, urinary, male genital, and other systems.[1,3,40,48] Deaths ascribed to DS alone, which are included with congenital anomalies under *ICD-9* coding (but excluded in this study), were found in a Canadian study[61] to be primarily due to pneumonia and congenital heart disease.

In summary, our record-linkage study of DS in cohorts from Sweden and Denmark revealed elevated risks of incident leukemia and (based on small numbers) testicular, penile, and liver cancers, as well as excess mortality ascribed to leukemia, stomach cancer, and numerous nonmalignant causes of death, including dementia or Alzheimer disease, epilepsy, ischemic heart disease, other heart disease, cerebrovascular disease, infectious diseases, respiratory diseases, and congenital anomalies. The precise magnitude of the risks to individuals with DS could not be estimated, as we included only events occurring more than 1 year subsequent to a hospital discharge. However, the increased risks of incident acute leukemia in this investigation were in agreement with estimates from previous population-based studies,[6,19,20] whereas most of the excess causes of death observed in this investigation have been described in previous surveys and seem biologically plausible. Our findings differ somewhat from those of a US DS death certificate study, possibly because of differences in the source of the population (deaths only) and the methods of analysis.[62] Because hospitalized Swedish and Danish patients with DS have been followed for only 10 years on average, further follow-up is needed to clarify cancer and mortality risks as the population ages. Chromosome 21 genes acting in conjunction with other genes or environmental exposures may modify disease risks among those with DS. In particular, the altered immunologic and other host factors may render those with DS more susceptible to environmental exposures such as infectious agents, including those prevalent in institutionalized populations. Down syndrome may represent a model of the interaction between candidate genes and exposures that may deepen our understanding of disease mechanisms in individuals affected and unaffected by DS.

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